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GENIUS-CHD Consortium

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# Relations between lipoprotein(a) concentrations, LPA genetic variants, and the risk of mortality in patients with established coronary heart disease: a molecular and genetic association study

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## Summary

**Background** Lipoprotein(a) concentrations in plasma are associated with cardiovascular risk in the general population. Whether lipoprotein(a) concentrations or LPA genetic variants predict long-term mortality in patients with established coronary heart disease remains less clear.

**Methods** We obtained data from 3313 patients with established coronary heart disease in the Ludwigshafen Risk and Cardiovascular Health (LURIC) study. We tested associations of tertiles of lipoprotein(a) concentration in plasma and two LPA single-nucleotide polymorphisms ([SNPs] rs10455872 and rs3798220) with all-cause mortality and cardiovascular mortality by Cox regression analysis and with severity of disease by generalised linear modelling, with and without adjustment for age, sex, diabetes diagnosis, systolic blood pressure, BMI, smoking status, estimated glomerular filtration rate, LDL-cholesterol concentration, and use of lipid-lowering therapy. Results for plasma lipoprotein(a) concentrations were validated in five independent studies involving 10 195 patients with established coronary heart disease. Results for genetic associations were replicated through large-scale collaborative analysis in the GENIUS-CHD consortium, comprising 106 353 patients with established coronary heart disease and 19 332 deaths in 22 studies or cohorts.

**Findings** The median follow-up was 9.9 years. Increased severity of coronary heart disease was associated with lipoprotein(a) concentrations in plasma in the highest tertile (adjusted hazard ratio [HR] 1.44, 95% CI 1.14–1.83) and the presence of either LPA SNP (1.88, 1.40–2.53). No associations were found in LURIC with all-cause mortality (highest tertile of lipoprotein(a) concentration in plasma 0.95, 0.81–1.11 and either LPA SNP 1.10, 0.92–1.31) or cardiovascular mortality (0.99, 0.81–1.2 and 1.13, 0.90–1.40, respectively) or in the validation studies.

**Interpretation** In patients with prevalent coronary heart disease, lipoprotein(a) concentrations and genetic variants showed no associations with mortality. We conclude that these variables are not useful risk factors to measure to predict progression to death after coronary heart disease is established.

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## Introduction

Worldwide, cardiovascular disease remains the leading cause of death.<sup>1</sup> Lipoprotein(a) has been identified as a risk factor for cardiovascular disease and suggested as a potential therapeutic target based on independent

associations with atherosclerosis and cardiovascular events in general population studies.<sup>2,3</sup> A meta-analysis of 18 general population studies showed a combined risk ratio for coronary heart disease of 1.7 (95% CI 1.4–1.9) for people with lipoprotein(a) concentrations in the

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## Research in context

## Evidence before this study

Plasma lipoprotein(a) is a recognised emerging risk factor for coronary heart disease. We searched MEDLINE with the terms “lipoprotein(a)” and “lp(a)” to identify studies reporting on the association between lipoprotein(a) and cardiovascular risk published up to Dec 15, 2016. Several studies were identified that showed a clear association between increased concentrations of lipoprotein(a) in plasma and increased risk of atherosclerotic cardiovascular disease in general populations. In studies of patients with established coronary heart disease, however, the association was weak or absent, although populations were small and the studies were underpowered to assess this relation. Concentrations of lipoprotein(a) in plasma are genetically determined by two single-nucleotide polymorphisms (SNPs) in *LPA* loci (rs10455872 and rs3798220), which makes feasible exploration of the role of lipoprotein(a) in patients with coronary heart disease in large epidemiological and genetic association studies. Importantly, treatments for reducing lipoprotein(a) concentrations are also emerging. Thus, improved understanding of the role of lipoprotein(a) in this population would indicate whether lipoprotein(a) is likely to be a useful biomarker for risk stratification and treatment targets in patients with established coronary heart disease.

## Added value of this study

We investigated whether lipoprotein(a) concentrations in plasma and two *LPA* SNPs were associated with long-term mortality and disease severity in patients with established coronary heart disease. Our findings were validated or replicated in 29 independent cohorts involving 116 548 participants with long-term follow-up. Neither lipoprotein(a) concentrations nor *LPA* genetic variants were associated with cardiovascular or all-cause mortality. However, concentrations of lipoprotein(a) in the highest tertile and the presence of either *LPA* SNP were associated with increased severity of coronary heart disease.

## Implications of all the available evidence

Although observational data for measuring risk through stratification by lipoprotein(a) concentrations in general populations is robust, our findings raise questions about the usefulness of this biomarker in patients with established coronary heart disease. The reasons for this discrepancy need to be investigated. Treatments to reduce lipoprotein(a) concentrations are emerging, such as PCSK9 inhibitors and antisense agents, but whether lowering of lipoprotein(a) concentrations by drugs such as PCSK9 inhibitors has an added effect on cardiovascular outcomes beyond that mediated by their substantial reductions of LDL-cholesterol concentrations needs to be determined.

highest tertile compared with those who had concentrations in the lowest tertile.<sup>4</sup> The Copenhagen City Heart Study<sup>5</sup> showed a very similar risk estimate when comparing tertiles, and even higher risks once lipoprotein(a) concentrations exceeded the 90th percentile of the frequency distribution. In an individual-level meta-analysis of patients' records, participants with a history of cardiovascular disease at baseline were excluded.<sup>6</sup> A continuous, although modest, relation between lipoprotein(a) concentrations and the incidence of coronary heart disease and stroke was found in this general population, with frequencies of events per 1000 person-years being 5·6 (95% CI 5·4–5·9) and 4·4 (4·2–4·6) in the highest and lowest tertiles of lipoprotein(a) concentrations, respectively.

Lipoprotein(a) is composed of an LDL-like core containing apolipoprotein B, to which one copy of the apolipoprotein(a) glycoprotein is attached by a disulfide bridge.<sup>7–9</sup> The physiological function of lipoprotein(a) is unknown, as are the precise mechanisms of synthesis and catabolism. Assembly is thought to be on the surface membrane of hepatocytes,<sup>10</sup> and several cell-surface receptors have been implicated in its catabolism.<sup>11</sup> Lipoprotein(a) might have effects on the vascular tree similar to those of LDL, but it is postulated to be more atherogenic because of specific prothrombotic effects.<sup>3</sup> Circulating concentrations of lipoprotein(a) vary widely and are related to the number of kringle IV type 2 repeats and other sequence variants in the *LPA* gene.<sup>12,13</sup> Two

common *LPA* single-nucleotide polymorphisms (SNPs), rs10455872 (intronic non-coding) and rs3798220 (missense variant Ile4399Met in the apolipoprotein(a) protease-like domain), explain much of the variation in lipoprotein(a) concentrations, and are linked to the risk of incident myocardial infarction.<sup>14,15</sup>

Unlike many other traditional risk factors for coronary heart disease, lipoprotein(a) is difficult to modify by lifestyle changes.<sup>3</sup> PCSK9 inhibitors reduce concentrations of lipoprotein(a) by 20–30%,<sup>16</sup> but are not yet routinely used for this purpose. Lipoprotein apheresis is the only available approach to substantially lower lipoprotein(a) concentrations.<sup>3</sup>

The relation between increased lipoprotein(a) concentrations and future or recurrent cardiac events in patients with established coronary heart disease has been less extensively studied than the relation in people in the general population, but so far seems weaker. Furthermore, risk might be modified by LDL-cholesterol concentration.<sup>4,17,18</sup> We aimed to assess systematically whether lipoprotein(a) and two *LPA* SNPs are associated with long-term mortality and disease severity in a large population of patients with established coronary heart disease.

## Methods

## Patients

Between 1997 and 2000, 3313 German patients scheduled to undergo coronary angiography were enrolled in the

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Ludwigshafen Risk and Cardiovascular Health (LURIC) study.<sup>19</sup> The study design and examinations at baseline have been described elsewhere.<sup>19</sup> Participants with acute illnesses other than acute coronary syndromes, such as malignancy or other chronic non-cardiac diseases, within the previous 5 years were excluded. Clinically stable patients without acute coronary syndromes who had coronary angiogram data were enrolled. Information on death during follow-up was obtained from the local public health departments. Cardiovascular mortality was defined as death due to fatal myocardial infarction, sudden cardiac

death, death after cardiovascular intervention, stroke, and other deaths caused by cardiovascular diseases.

The study was done in accordance with the Declaration of Helsinki and approved by the responsible ethics committee of Ärztekammer Rhineland-Palatinate, Germany. Written informed consent was obtained from all patients. No patients were lost to follow-up.

### Lipoprotein(a) validation cohorts

We compared our findings for associations with lipoprotein(a) concentrations in plasma with those from

	All patients (n=3313)	Lp(a) tertile 1 ≤10.0 mg/dL (n=1146)	Lp(a) tertile 2 10.1–26.0 mg/dL (n=1065)	Lp(a) tertile 3 >26.0 mg/dL (n=1102)	p value*
Age	62.7 (10.6)	62.8 (10.7)	62.8 (10.7)	62.4 (10.4)	0.445
Sex					
Male	2308 (70%)	842 (74%)	735 (69%)	731 (66.3%)	0.001
Female	1005 (30%)	304 (27%)	330 (31%)	371 (33.7%)	0.001
BMI (kg/m <sup>2</sup> )	27.5 (4.1)	27.5 (4.1)	27.7 (4.2)	27.2 (3.9)	0.066
Systolic blood pressure (mm Hg)	141 (24)	142 (23)	140 (24)	141 (24)	0.184
Lipoprotein(a) concentration in plasma (mg/dL)	16.0 (0.5–31.5)	5.0 (1.8–8.2)	16.0 (12.5–19.6)	58.0 (35.7–80.4)	<0.0001
LPA SNP minor allele†					
Any	524 (16%)	73 (6%)	81 (8%)	370 (34%)	<0.0001
rs10455872 A/G	399 (13%)	56 (5%)	63 (6%)	280 (28%)	<0.0001
rs10455872 G/G	10 (<0.5%)	0	1 (<0.5%)	9 (1%)	<0.0001
rs3798220 T/C	124 (3.8%)	17 (2%)	19 (2%)	88 (8%)	<0.0001
rs3798220 C/C	1 (<0.5%)	0	0	1 (<0.5%)	..
Lipid profile					
Total cholesterol (mg/dL)	192 (39)	189 (39)	191 (38)	197 (40)	<0.0001
Triglycerides (mg/dL)	173 (118)	179 (136)	173 (115)	167 (99)	0.089
HDL cholesterol (mg/dL)	39 (11)	38 (11)	39 (11)	39 (10)	0.037
LDL cholesterol (mg/dL)	117 (34)	112 (34)	116 (33)	122 (36)	<0.0001
VLDL cholesterol (mg/dL)	37 (26)	39 (30)	36 (26)	36 (24)	0.002
Apolipoprotein B (mg/dL)	104 (25)	103 (24)	103 (24)	107 (25)	<0.0001
HbA <sub>1c</sub> (%)	6.3 (1.2)	6.3 (1.4)	6.3 (1.2)	6.3 (1.2)	0.203
HbA <sub>1c</sub> (mmol/mol)	43 (13)	45 (15)	45 (13)	45 (13)	0.203
eGFR (mL/min/1.73 m <sup>2</sup> ) ‡	81.7 (20.1)	82.1 (20.7)	81.5 (20.1)	81.4 (19.6)	0.602
hsCRP (mg/L)	3.4 (0.7–1.0)	3.6 (0.7–8)	3.4 (0.7–0)	3.2 (0.6–4)	0.037
Interleukin 6 (ng/L)	3.2 (1.0–5.4)	3.3 (0.9–5.7)	3.2 (1.1–5.3)	3.2 (1.1–5.3)	0.235
Fibrinogen (mg/dL)	377 (311–433)	370 (299–411)	380 (316–444)	381 (319–443)	0.619
Friesinger score	5.4 (3.9)	5.1 (3.9)	5.2 (4.0)	5.9 (3.8)	<0.0001
Coronary heart disease	2580 (78%)	867 (76%)	810 (76%)	903 (82%)	0.0004
Previous myocardial infarction	1365 (41%)	446 (39%)	448 (42%)	471 (43%)	0.144
Diabetes	1322 (40%)	467 (41%)	440 (41%)	415 (38%)	0.170
Taking lipid-lowering therapy	1607 (49%)	489 (43%)	529 (50%)	589 (53%)	<0.0001
Current or ex-smoker	2120 (64%)	741 (65%)	681 (64%)	698 (63%)	0.808
Hypertension	2409 (73%)	826 (72%)	762 (72%)	821 (75%)	0.255
Death from any cause	994 (30%)	361 (32%)	322 (30%)	311 (28%)	0.233
Cardiovascular deaths	621 (19%)	232 (20%)	186 (18%)	203 (19%)	0.129

Data are mean (SD) number (%), or median (IQR). Lp(a)=lipoprotein(a). SNP=single-nucleotide polymorphism. eGFR=estimated glomerular filtration rate. hsCRP=high sensitivity C-reactive protein. \*Comparison between tertiles of Lp(a). †Ten participants carried minor alleles in LPA SNPs rs10455872 and rs3798220. Any LPA SNP minor allele information was available in 3287 participants. LPA SNP rs10455872 data were available in 3058 participants. LPA SNP rs3798220 data were available in 3286 participants. No information on LPA SNPs was available in 23 participants. ‡Calculated with the Chronic Kidney Disease Epidemiology Collaboration formula.

**Table: Baseline characteristics of LURIC study participants**

10195 participants in five independent prospective studies: the Homburg Cream and Sugar (HCS) study, the KAROLA study, the WENBIT/WECAC study, the PROSPER study, and the ATHEROGENE study (appendix pp 1–3). These studies were selected because of good matches for inclusion criteria and comparable cardiovascular endpoints available. Following the strategy of a previous meta-analysis,<sup>4</sup> we separated lipoprotein(a) concentrations into tertiles to minimise the effects of different methods of measurement.

### Genetic associations

Positive *LPA* SNP carrier status was defined as heterozygosity or homozygosity for the minor alleles of rs10455872, rs3798220, or both. Associations for the two *LPA* SNPs with all-cause and cardiovascular mortality from LURIC were validated by collaborative analysis through the Genetics of Subsequent Coronary Heart Disease (GENIUS-CHD) consortium at the individual participant level.<sup>20</sup> This grouping of multiple international studies brings together data from patients with coronary heart disease, including stable disease and acute coronary syndromes, who have blood or tissue samples stored for analysis or genotyping data, and prospective follow-up data for subsequent events, including cardiovascular events and death. We compared our genetic findings with those in studies and cohorts with available data for *LPA* SNP (appendix p 1).

### Laboratory methods and procedures

In LURIC, blood samples were taken on the day of coronary angiography for measurement of lipoprotein(a) concentrations in plasma with the *LPA* Test (Rolf Greiner Biochimica, Flacht, Germany). Details of laboratory methods for the other studies and cohorts are described in the appendix (pp 3–5).

### Statistical analysis

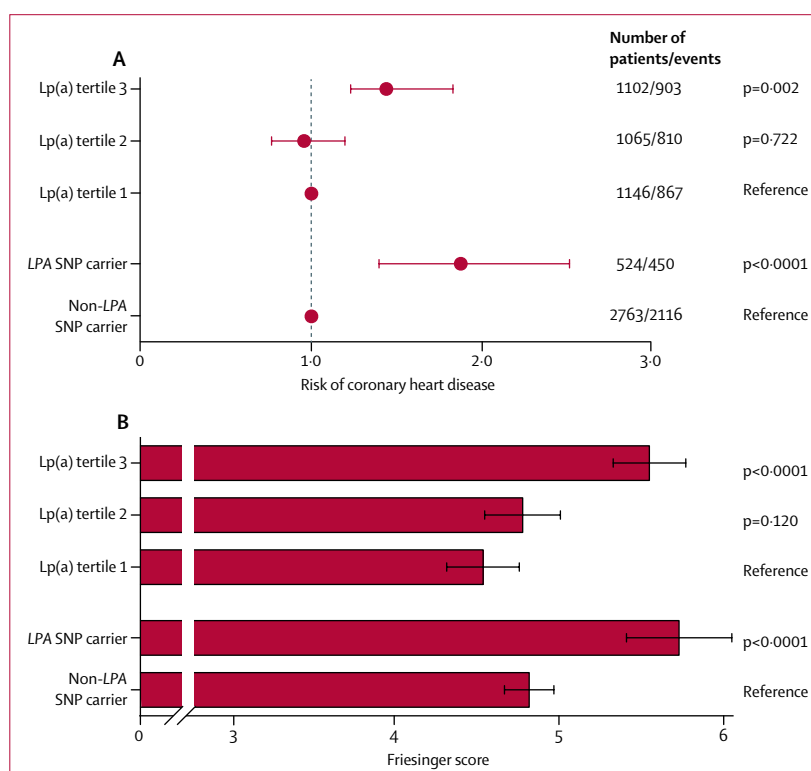
Continuous data are presented as means and SDs when normally distributed or as medians and IQRs for variables with skewed distributions. Categorical data are presented as numbers and percentages. Statistical differences between continuous variables were determined with one-way ANOVA, and between categorical variables with the Kruskal-Wallis test or the  $\chi^2$  test. In analyses of the associations, models were analysed with and without adjustment for age, sex, diabetes diagnosis, systolic blood pressure, BMI, smoking status, estimated glomerular filtration rate (eGFR), and LDL-cholesterol concentration.

Associations between tertiles of lipoprotein(a) concentrations in plasma and *LPA* SNP carrier status with all-cause and cardiovascular mortality in the LURIC study were assessed with Cox regression analyses. We did sensitivity analyses to determine the association between lipoprotein(a) concentrations in plasma and mortality in patients receiving statins or no statins and for those with

LDL-cholesterol concentrations of 130 mg/dL or less versus more than 130 mg/dL. Moreover, to assess the degree of variance in lipoprotein(a) concentrations caused by the *LPA* SNPs rs10455872 and rs3798220, we calculated  $\eta^2$ . Associations between tertiles of lipoprotein(a) and *LPA* SNP carrier status and risk of coronary heart disease or severity of coronary heart disease were assessed with logistic regression analyses or linear regression analyses, respectively.

In the lipoprotein(a) concentration validation studies, we also used Cox regression analyses to assess the association between tertiles of lipoprotein(a) and each study's composite cardiovascular endpoints. To analyse the association between the two *LPA* SNPs and cardiovascular outcome in the GENIUS-CHD consortium, we did meta-analyses with log hazard ratios (HRs) and SEs derived from unadjusted Cox regression models of the association between the SNPs and fatal cardiovascular events and all-cause mortality from every cohort included. Standard normal random-effects meta-analysis was done with the R metaplan package (version 0.7.8). All other analyses were done with SPSS version 20.0. Data are presented as HRs or odds ratios (ORs) with 95% CIs.

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**Figure 1: Association between tertiles of lipoprotein(a) concentrations or *LPA* SNP carrier status and presence and severity of coronary heart disease in the LURIC study**

(A) Risk of coronary heart disease, presented as odds ratios and 95% CIs, as determined by logistic regression. (B) Severity of coronary heart disease, presented as marginal means and 95% CIs. 3313 participants were assessed for the Lp(a) tertiles and 3287 for the *LPA* SNP analysis. All analyses were adjusted for age, sex, diabetes, systolic blood pressure, BMI, smoking status, estimated glomerular filtration rate, LDL-cholesterol concentration, and use of lipid-lowering therapy. Lp(a)=lipoprotein(a). SNP=single-nucleotide polymorphism.



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We assessed associations between the different tertiles of lipoprotein(a) concentration or *LPA* SNP carrier status and Friesinger score as a measure for the severity of coronary heart disease in LURIC. We used generalised linear models to estimate the marginal means of Friesinger score and made adjustments for age, sex, diabetes diagnosis, systolic blood pressure, BMI, smoking status, eGFR, LDL-cholesterol concentration, and the use of lipid-lowering therapy.

### Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

### Results

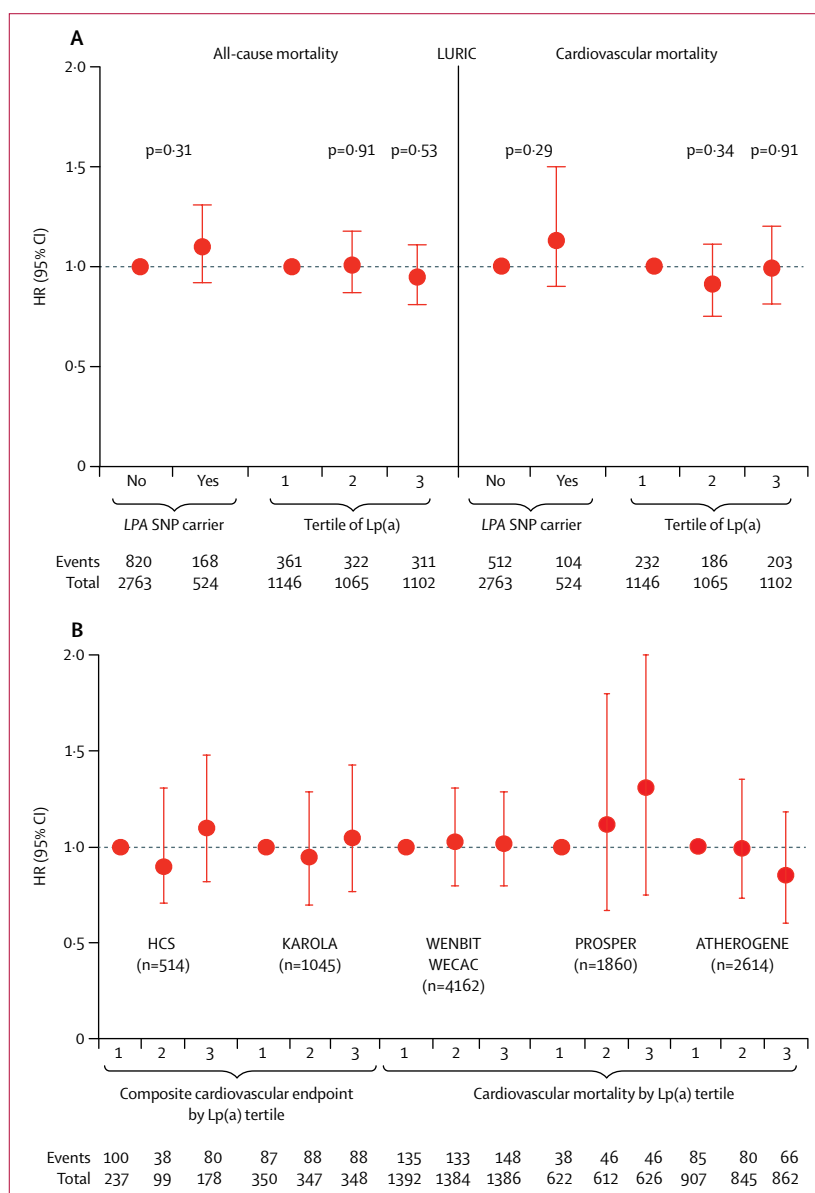
3313 participants in the LURIC study with established coronary heart disease, lipoprotein(a) measurements, and genotyping data were included in these analyses (table). 10195 patients were included in the five independent studies of cardiovascular mortality and lipoprotein(a) concentrations in plasma (appendix pp 10–14), and data were available for 106353 patients with established coronary heart disease and 19332 deaths in 22 studies or cohorts from the GENIUS-CHD consortium (appendix pp 21–22).

The prevalence of most traditional cardiovascular risk factors (age, reduced eGFR, diabetes type 1 and type 2, smoking, and hypertension) among participants in the LURIC study did not differ significantly across tertiles of lipoprotein(a) concentration. Significant differences were noted for LDL-cholesterol concentration and distribution of male or female sex. The prevalence of coronary heart disease at baseline was 78%. Among patients with lipoprotein(a) concentrations in the highest tertile, the prevalence of angiographically defined coronary heart disease was significantly greater than among those with concentrations in the lowest tertile (table).

Among participants in LURIC, data on rs10455872 were available for 3058 and on rs3798220 for 3286. 524 (16%) participants carried any minor allele, of whom ten carried minor alleles in both SNPs (table). The frequencies of minor alleles increased with increasing tertile of lipoprotein(a) concentration (table). Of note, we saw an almost linear increase in the number of minor alleles with increasing median concentration of lipoprotein(a) in plasma ( $p<0.0001$ ), and for each *LPA* SNP minor allele carried the median lipoprotein(a) concentration was increased by 250% (appendix p 23).

Compared with patients who had lipoprotein(a) concentrations in the lowest tertile, the risk for angiographic coronary heart disease in the LURIC study was significantly increased for those with concentrations in the highest tertile (adjusted HR 1.44, 95% CI 1.14–1.83; figure 1, appendix p 7). Similar results were obtained for carriers of any *LPA* SNP (adjusted OR 1.88, 95% CI 1.40–2.53 appendix p 6). Increased concentrations of lipoprotein(a) in plasma and being a carrier of one or more *LPA* SNP minor alleles were associated with increased severity of coronary heart disease (figure 1).

During a median follow-up of 9.9 years, 994 (30%) patients in the LURIC study died. 621 (19%) deaths were classified as cardiovascular disease-related deaths. We found no association between all-cause or cardiovascular mortality and any tertile of lipoprotein(a) concentration,



**Figure 2: Association between tertiles of lipoprotein(a) concentration, *LPA* SNP carrier status, and mortality or cardiovascular endpoints**

(A) All-cause and cardiovascular mortality in participants of the LURIC study. P values are for *LPA* SNP carrier yes vs no and for Lp(a) tertile 2 or 3 vs tertile 1. (B) Composite cardiovascular endpoints and cardiovascular mortality in validation studies. All values were calculated with Cox regression analysis adjusted for age, sex, diabetes, systolic blood pressure, BMI, smoking status, estimated glomerular filtration rate, LDL-cholesterol concentration, and use of lipid-lowering therapy. HR=hazard ratio. SNP=single-nucleotide polymorphism. Lp(a)=lipoprotein(a).

in the crude or adjusted models (figure 2, appendix p 8). In our sensitivity analyses, this association was not modified by LDL-cholesterol concentration or statin treatment (appendix p 9).

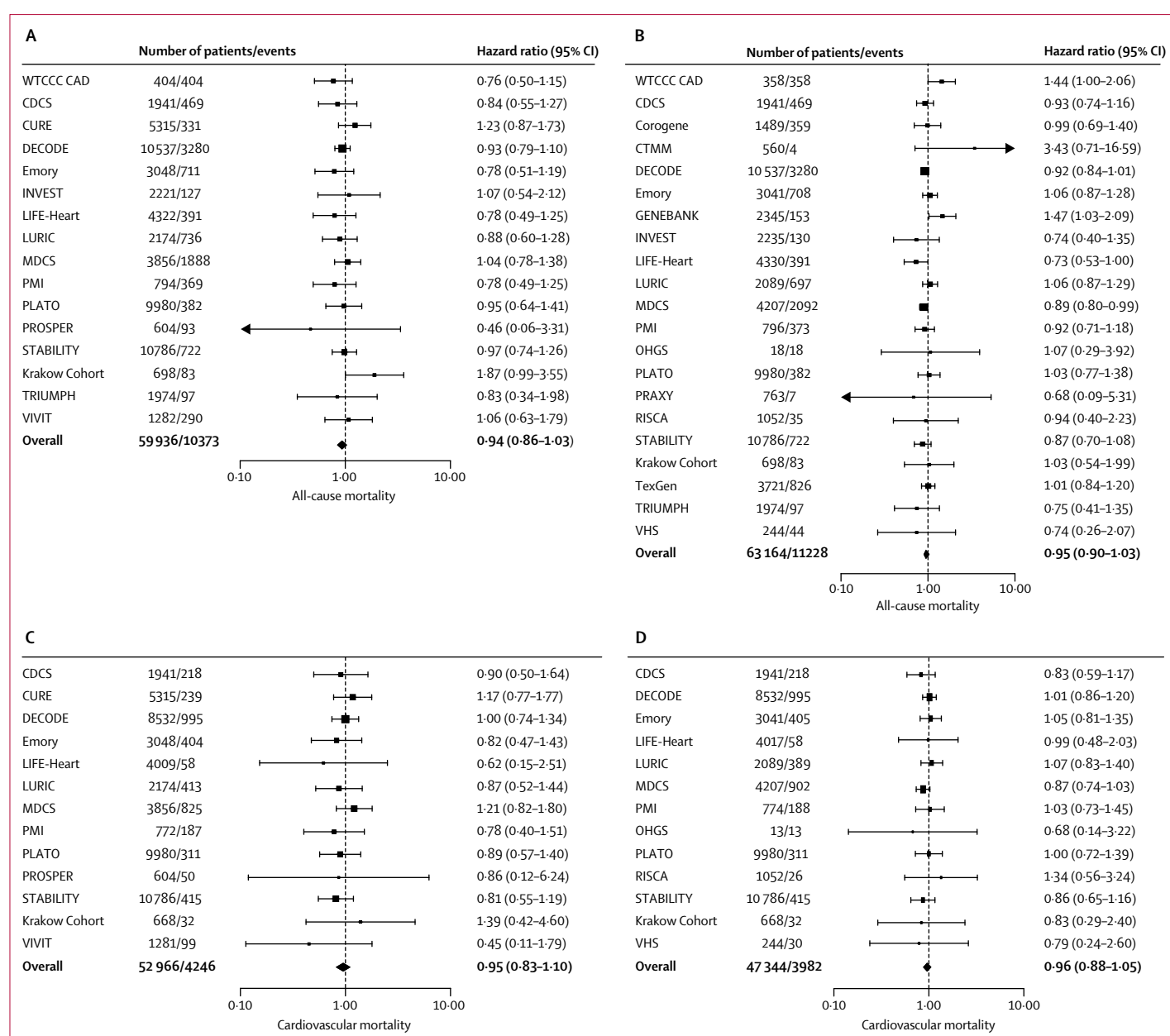
In the five independent studies of cardiovascular mortality and lipoprotein(a) concentrations in plasma, no associations were found between tertiles of lipoprotein(a) concentrations and the composite cardiovascular endpoints or cardiovascular mortality (figure 2, appendix pp 15–19).

We found no association between *LPA* SNPs and all-cause or cardiovascular mortality in LURIC (figure 2, appendix p 20). Likewise, in the validation studies and cohorts from the GENIUS-CHD consortium, neither rs10455872 nor rs3798220 was associated with increased all-cause or cardiovascular mortality (figure 3).

## Discussion

Among patients in the LURIC study with established coronary heart disease, the concentration of lipoprotein(a)

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**Figure 3:** Forest plots of risk ratios for all-cause and cardiovascular mortality in studies of the GENIUS-CHD consortium

All-cause mortality associated with *LPA* single-nucleotide polymorphisms rs3798220 (A) and rs10455872 (B). Cardiovascular mortality associated with *LPA* SNPs rs3798220 (C) and rs10455872 (D). Markers represent point estimates of risk ratios and horizontal bars indicate 95% CIs. Marker size represents study weight in random-effects meta-analysis.

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in plasma at the time of recruitment and the number of minor alleles at two biallelic SNPs in *LPA* loci were positively related to the presence and severity of coronary heart disease, which supports findings in previous case-control or cross-sectional studies involving patients with or without prevalent cardiovascular disease.<sup>14,21,22</sup> By contrast, neither lipoprotein(a) concentrations nor *LPA* SNPs were associated with cardiovascular or all-cause mortality during long-term follow-up. These findings were validated in 27 studies and cohorts that included 116 548 participants.

The association between lipoprotein(a) and coronary heart disease, which is independent of traditional cardiovascular risk factors, has been known for many years.<sup>4–6,23–25</sup> It is based on findings mainly from studies of apparently healthy participants in the general population<sup>4–6,25</sup> rather than from investigations of patients with established coronary heart disease. Genetic diversity at the *LPA* locus, including the SNPs rs10455872 and rs3798220, has been associated with raised concentrations of lipoprotein(a) in plasma and incident cardiovascular disease.<sup>6,14</sup> *LPA* kringle IV type 2 repeats and raised lipoprotein(a) concentrations in serum have been associated with increased prevalence of coronary heart disease in a mendelian randomisation analysis.<sup>26</sup> The findings from previous studies and this analysis, therefore, support a causal link between lipoprotein(a) and atherosclerosis development.

The lack of a clear association between lipoprotein(a) concentrations or *LPA* variants and mortality in the LURIC population or in the 27 validation studies and cohorts raises the possibility that lipoprotein(a) concentration is a weaker risk factor in patients with coronary heart disease than in healthy people. This difference might be due to competing risks commonly seen in patients. In a meta-analysis, the risk ratio for coronary heart disease in the general population was 1.7 (95% CI 1.4–1.9) when the highest and lowest tertiles of lipoprotein(a) concentrations were compared, but was only 1.3 (1.1–1.6) for patients who had pre-existing comorbidities in nine studies (two of patients receiving dialysis, one of patients with diabetes, and six of patients with coronary heart disease).<sup>4</sup> Of note, however, the largest contributor of patients with comorbidities to that meta-analysis was the Scandinavian Simvastatin Survival Study,<sup>27</sup> which included patients with severe hypercholesterolaemia. These patients were not representative of the wider coronary heart disease population, having total cholesterol concentrations in the range of 212–309 mg/dL, but accounted for three-quarters of the comorbidity evidence in the meta-analysis. These total cholesterol concentrations are much higher than those in LURIC and the GENIUS-CHD populations. Generalisability of the findings of the meta-analysis to people with lower total cholesterol concentrations is, therefore, limited. Of the eight remaining studies in the meta-analysis, only one

reported a significant association between lipoprotein(a) and incident coronary heart disease.

A study of patients with established coronary heart disease showed a small but non-significant relation between lipoprotein(a) and future cardiovascular events among those with mean concentrations of LDL cholesterol higher than 130 mg/dL at baseline compared with patients who had lower concentrations.<sup>17</sup> The association between lipoprotein(a) concentration and cardiovascular events might, therefore, be modified by LDL-cholesterol concentration, and, beyond this, potentially by statin use. We did not detect such interactions in our analyses, but in LURIC the mean LDL-cholesterol concentration was 117 (SD 34) mg/dL at baseline, and in the GENIUS-CHD consortium studies the value was 130 (38) mg/dL. As such, we could not investigate an association between lipoprotein(a) and cardiovascular outcomes in patients with very high LDL-cholesterol concentrations. Adjustments for other established confounders investigated at baseline (age, sex, diabetes, systolic blood pressure, BMI, smoking status, estimated glomerular filtration rate, LDL-cholesterol concentration, and use of lipid-lowering therapy) also did not modify our findings, although we could not account for factors that might have changed during follow-up, such as LDL-cholesterol concentration. In Germany, however, adherence to statin regimens is poor and we suspect that an effect of time-dependent changes in LDL-cholesterol concentrations is unlikely, at least in the German cohorts included in our analysis.<sup>28</sup>

Our analysis had other limitations that should be taken into account. First, lipoprotein(a) concentrations in plasma were measured by different methods in LURIC and the validation cohorts. To minimise bias caused by differences in assay calibrations, we assessed all risk estimates in relation to tertiles of lipoprotein(a) concentrations. Nevertheless, we cannot entirely exclude the possibility that lipoprotein(a) concentrations in plasma were altered by the initial cardiovascular event itself or by changes during follow-up. Second, we focused only on all-cause and cardiovascular mortality, but other studies have combined various fatal and non-fatal cardiovascular events.<sup>4–6,17</sup> Exclusion of non-fatal events arguably keeps to a minimum the effects of differences between studies and changes over time in definitions and methods of assessment.<sup>29</sup> This approach might have reduced the statistical power to detect differences between populations due to the number of events being reduced, meaning we could have missed small effect sizes. A type 2 error remains possible, but, owing to the sample size afforded by the use of independent study cohorts, we anticipate this risk to be minimal. Nevertheless, we cannot rule out that extreme concentrations of lipoprotein(a) (ie, 50 mg/dL), beyond which the recent European Society of Cardiology and European Atherosclerosis guideline deems risk to be high,<sup>30</sup> would have effects. Finally, we could not compare



effects of lipoprotein(a) concentrations or genetic variants on risk of subsequent non-fatal events with those on fatal events, which could have been of interest given that such differences have been described for other risk factors.<sup>31</sup> Ischaemic events, thrombotic events, or both—fatal and non-fatal—might be more specifically related to lipoprotein(a) than cardiovascular deaths overall. These relations will need to be studied further as outcome data emerge, particularly since lipoprotein(a) concentrations seemed in previous analyses to have similar associations with fatal coronary heart disease and non-fatal myocardial infarction in patients without established coronary heart disease.<sup>6</sup>

The results from this and previous studies suggest that lipoprotein(a) concentrations and *LPA* SNPs promote early development of atherosclerosis and severe coronary heart disease. Furthermore, patients with established coronary heart disease who carry SNPs associated with increased concentrations of lipoprotein(a) are more likely to have earlier onset of disease and be more susceptible to atherosclerotic manifestations outside of the coronary tree than patients without SNPs,<sup>21</sup> which supports a role of lipoprotein(a) in atherosclerosis progression. The lack of association between lipoprotein(a) and cardiovascular mortality in this study was surprising and is a finding that we cannot explain. Among the possible explanations are index event biases or survival biases. We cannot fully exclude these possibilities, although they are unlikely to have affected our findings substantially because the frequencies of *LPA* SNP minor allele were the same in our and the control populations, and in the PROCARDIS and other cohorts.<sup>14</sup> Additionally, the characteristics of patients were well balanced across genotypes. Of note, although lipoprotein(a) concentrations would not be useful for predicting mortality, patients with coronary heart disease and high lipoprotein(a) concentrations might still benefit from lipid-lowering treatment, as it might slow disease progression.

Screening for increased concentrations of lipoprotein(a) is recommended in people at intermediate or high risk of cardiovascular disease or coronary heart disease.<sup>3</sup> In view of the broad evidence in favour of lipoprotein(a) as a marker of risk in clinically healthy people,<sup>3,24</sup> our data suggest that integration of lipoprotein(a) into risk stratification in primary rather than in secondary prevention might be more useful. We acknowledge that detection of very high concentrations of lipoprotein(a) in plasma in patients with established coronary heart disease could be helpful to trigger screening of family members to improve early preventive measures for carriers of *LPA* genetic variants.

Interventions that lower concentrations of lipoprotein(a) are scarce. Additionally, whether lowering of lipoprotein(a) concentrations by drugs such as PCSK9 inhibitors has an added effect on cardiovascular outcomes beyond that mediated by their substantial reductions of LDL-cholesterol concentrations needs to

be determined.<sup>16</sup> More specific therapies targeting lipoprotein(a) directly, such as antisense oligonucleotides, are being developed and tested,<sup>32</sup> and findings of these studies might make clearer the usefulness of reducing lipoprotein(a) concentrations.

Concentrations of lipoprotein(a) in plasma and genetic variants were strongly associated with the presence and severity of coronary heart disease, but neither predicted the risk of cardiovascular or all-cause mortality in patients with established disease. Although the discrepancy in these findings with those in general populations, where lipoprotein(a) increases risk of a first coronary heart disease event, requires further investigation, our data suggest that use of lipoprotein(a) as a risk marker might be useful to predict onset of coronary heart disease rather than progression to death after a coronary heart disease event.

#### Contributors

SZ, UL, DR, SB, RBS MSN, AMR, RND, RC-D, JJ, FB, LW, IK, AH, HS, WM, and TSp designed the study. SZ, MEK, AFS, KD, UL, CWe, WK, DR, UM, LPB, HB, RTJ, STri, MKI, SB, CS, RBS, KJL, ON, GFTS, GST, JS, RL, NS, JWJ, GD, TSt, APP, VAC, AMR, RND, RC-D, JJ, MSc, FB, JT, JGS, RM, SC, JAS, OO, DG, NM, AL, CHS, HD, AM, PSB, CPN, NJS, IEH, GP, AAQ, Y-AK, JAH, HA, WHWT, SLH, CH, EH, AFRS, AS, LW, AA, IK, CL, LP, JCE, JMB, PB, WS, MKa, MSa, SSV, CMB, V-VL, EB, BDH, AH, FWA, HS, WM, and TSp collected data. SZ, MEK, ROM, AFS, KD, CWe, DR, UM, HB, RTJ, IP, STri, MKI, AF, CWe, CS, EV, ON, ERP, GST, JS, RL, STro RAJS, NS, HVG, GD, TSt, VAC, YG, MSc, FB, JT, JGS, ROV, SC, PAL, OO, DG, NM, AL, CHS, HD, AM, PSB, CPN, NJS, DK, AAQ, Y-AK, JAH, HA, SLH, NE, CH, CL, LP, JCE, JMB, GT, PB, WS, MKa, MSa, SSV, V-VL, EB, BDH, AH, FWA, HS, DF, and TSp analysed the data. SZ, MEK, ROM, AFS, KD, UL, WK, DR, UM, LPB, HB, RTJ, IP, STri, MKI, CS, RBS, ON, ERP, GST, NS, RL, TStro, RAJS, NS, JWJ, GD, VAC, YG, RC-D, JJ, MSc, JT, SC, CPN, NJS, AAQ, Y-AK, JAH, HA, SLH, CH, EH, LW, AA, CL, LP, JCE, JMB, GT, PB, MKa, V-VL, EB, MVH, BDH, AH, FWA, BKK, HS, DF, WM, and TSp interpreted the data. SZ, MEK, WK, UL, MKI, GD, YG, RC-D, JJ, AA, AH, FWA, RSP, BKK, DF, WM, and TSp wrote the paper. SZ, MEK, ROM, AFS, KD, CWe, DR, UM, LPB, HB, RTJ, IP, STri, MKI, AF, CS, ON, GST, GFTS, ERP, MSN, STro, RAJS, NS, JWJ, HVG, GD, APP, VAC, AMR, RND, MCs, JT, RM, SC, JAS, OO, DG, NM, CPN, NJS, JAH, AAQ, Y-AK, WHWT, SLH, CH, LW, AA, AS, CL, LP, JCE, JMB, GT, PB, WS, MKa, MSa, SSV, CMB, V-VL, EB, MVH, BDH, AH, FWA, RSP, HS, DF, and TSp provided critical revision of the drafts. RSP coordinated data collection and analysis for the GENIUS-CHD consortium. VT was the main analyst of GENIUS-CHD and gathered, processed, pooled, and produced outputs with the data obtained from the GENIUS-CHD cohorts.

#### Declaration of interests

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See [Online](#) for appendix

For the GENIUS-CHD consortium see <http://www.genius-chd.com>

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